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EXAMINER	
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ART UNIT	PAPER NUMBER
1619	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/351,862	Thorpe et al
Examiner	**Art Unit**
SHAHNAM SHARAREH	1619

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 20, 2001*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-30 and 34-38* is/are pending in the application.

4a) Of the above, claim(s) *2, 13, 16-18, 30, and 34-38* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-12, 14, 15, and 19-29* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3, 10 (A2)
5, 6, 7, 5½, 10, 12½, 15

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Amendment filed on February 22, 200, Paper No. 14 has been entered. Claims 1-30, 34-38 are pending. Applicant's election with traverse of Group I invention and the election of species "a second anti-cancer agent", "apoptosis-inducing agents", "monoclonal antibodies or fragments that bind to phosphatidylserine" is acknowledged. Applicant has not elected a species specifying the cytotoxic agent of the antibody-therapeutic agent construct directed to claims 23-29. Nevertheless, Examiner withdraws the requirement for election of this species to further expedite the prosecution. Accordingly, the search is now directed to the elected species of the generic claim 1 encompassing kits comprising an antibody that binds to phosphatidylserine and an anti-cancer agent comprising an apoptosis-inducing agent.

The election made on Paper No. 14 has not properly identified the claims that is elected consonant with this species requirement. As stated by Applicants the claimed invention is directed to at least one antibody or antigen binding fragment thereof that binds to an amino phospholipid in combination with either a detectably labeled antibody that binds to an amino phospholipid or at least a second anti-cancer agent. Applicant has elected the species "second anti cancer agent". Only claims 1, 3-11, 14-15, 19-29 are readable to the elected species. All other claims are directed to compositions having a detectably-labeled antibody, which is not elected.

Applicants' traversal in second restriction requirement has been fully considered and are found persuasive, claims 12-13 are rejoined, however, claim 13 is directed to an non-elected species because the at least first antibody does not bind the elected amino phospholipid.

Claims 2, 13, 16-18, 30-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 14. Claims 1-30, 34-38 are pending, however, claims 1-12, 14-15, 19-29 are under consideration at this time.

This application contains claim 2, 13, 16-18, 30-38 drawn to an invention nonelected with traverse in Paper No. 14 . A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-12, 14-15, 19-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 recitation of the phrase "biologically effective amounts" is indefinite, because it is not clear to what type of effect is the claimed amount directed? For what purpose is this amount effective? The metes and bounds of the claim is not clear.

In claims 1, 6-7, 10-11, 20-21, 23, 25-28, the recitation "fragment thereof" is indefinite. It is not clear to what antigen-binding moieties is applicant referring?

Claim 1 recites the limitation of at least a "second anti-cancer agent" while there was no first anti-cancer agent has been recited. This recitation appears vague.

Claim 9, 27 recite the phrase "operatively attached". It is not clear what is meant by this phrase or what type of chemical linkages are encompassed in the claimed invention.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-12, 14-15, 19-29 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions and kits comprising a first antibody directed to amino phospholipid, does not reasonably provide enablement for kits having antigen-binding fragments thereof that binds amino phospholipid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

First, there is no teaching nor is there any working examples identifying the various types of antibody fragments that maybe used to for practicing the instant kits. The specification has

not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass polypeptide which have amino acid substitutions other than the positions taught in the specification.. The specification broadly describe said fragments as intact antibody, antibody multimer, or anyone of variety of functional antigen binding regions of an antibody that may be used. Such teaching constitutes numerous possible amino acid sequences which are not supported by the instant disclosure. There is no guidance in the specification as to what alterations result in a functional fragments.

Second, the state of art is unpredictable in with respect to the use of instant antibodies and fragment's thereof for cancer treatment. Applicant's attention is drawn to Fishman et al (International Journal of Oncology 1997, (10):901-904). As indicated Professor Fishman specifically raises the question that autoantibodies (a species of claimed antibodies) directed to aminophosphalipids may induce an autoimmune disease (see page 903). Therefore, there can not be predictability in the art with respect to the scope of claimed fragments of such antibodies. Specifically, there is no dosing information neither is there any teachings provided in respect to the side effect profile, safety and specific utility of the instant fragments. Even further, there is no teaching how the data provided permits the determination of an effective amount of the claimed fragments for practicing the instant kits. Because of this lack of guidance, there would be a need for extended experimentation to determine which substitutions would be acceptable to retain functional activity.

Finally, the relationship between the sequence of a peptide and its tertiary structure (i.e., its activity) are not well understood and are therefore not predictable (Ngo et al. The Protein Folding Problem and Tertiary Structure Prediction, Merz & LeGrand, Birkhauser Boston, pages 491-495, 1994, entire article, especially Section 6, paragraph 1) or Skolnick (see Skolnick, Trends in Biotech, 2000). The instant claimed fragments are directed to unknown chains of polypeptide, thus, it would require undue experimentation for one of skill in the art to arrive at other amino acid sequences that would have the desirable functional activity. In other words, since it would require undue experimentation to identify amino acid sequences that have functional activity, it would require undue experimentation to make the corresponding pharmaceutical compositions and kits thereof.

Thus, in view of the lack of unpredictability in the art, the lack of working examples, and the lack of guidance in determining which fragments the enablement provided by the specification is not commensurate with the scope.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-12, 14-15, 19-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman et al (IDS, 2/14/2000) and Umeda (IDS, 9/19, 1999) in view of Haung et al Science 275: 547 - 550 1997 (IDS September 1999), and Blankenberg et al US patent 6,197,278 (IDS March 23, 2001) and WO 98/29453 ('453) (IDS 1/24/2000).

Fishman discloses anti-phospholipid antibodies directed to melanoma cells and other the cancer cells having over expressed outer membrane phophatidylserine (abstract). Fishmann teaches the potential use of autoantibodies in diagnostic and therapeutic area (abstract). Fishmann also teaches the use of antiphospholipid for various types of cancer cells exhibiting phophatidylserine on the outer cell membrane such as squamous cell carcinoma of the skin or ertythorleukemia (page 903). Finally, Fishman propose a new concept for the relationship between cancer and autoimmunity.

Umeda teaches methods of producing monoclonal antibodies directed to phosphatidylserine of plasma membrane, and that patients with malignancy have a higher titer of anti-PS antibodies (see abstract, page 2273; 2col, 2nd paragraph, 2276). Umeda's teachings is

used to show the conventional practice of preparing monoclonal antibodies directed to phosphatidylserine of outer cell membrane.

Huang et al disclose methods of occluding tumor vasculature in solid tumors of mice by targeting the cell surface domain of tumor vascular endothelial cells with a bispecific antibody-tissue factor conjugate (abstract, page 549). Huang et al specifically teach that administration of a drug acting on the tumor cells and selective blood coagulation of tumor vasculature can improve efficacy of antivascular therapy of solid tumors (page 549, 3rd col). Huang, however, does not specifically teach targeting of aminophospholipids

Blankenberg et al teaches Annexin as a peptide with high affinity to anionic phospholipid surface of the cell membrane. Blankenberg teaches targeting radio labeled Annexin V directed to a selected organ for any desired condition such as cancer (col 9 lines 50-65, col 12 lines 33-61, col 20 lines 41-55). Blankenberg doesn't teach the use of a second anti-cancer agent for therapeutic or diagnostic purposes.

'453 patent teaches peptide drugs with specific affinity towards phosphatidylserine. The drugs disclosed in '453 are used to treat or prevent immunological disorders involving blood coagulation. '453 doesn't teach therapeutic construct directed to solid tumors (abstract).

Although Fishmann or Umeda does not teach the combination of a anti- amino phospholipid antibody with a second anti-cancer agent for therapeutic kits, both WO patent and Blackenberg suggest methods and compositions that can be used for both therapeutic and imaging purposes. Further, Haung suggests that specific targeting of the tumor cell surface

markers with bispecific antibodies such as those directed to MHC class II can significantly improve the efficacy of coaguligand therapy, and finally Fishmann and WO '453 complement the teachings of Blackenberg and Haung because they show the general state of art for preparing peptide drugs and autoantibodies directed to aminophospholipids. Therefore, it would have been obvious to one of ordinary skill in the art at the time of invention to combine the teachings of Fishmann or Umeda, with Haung to enhance the cancer therapy of a solid tumor of interest, because both Fishman and Umeda suggest the potential benefits of such anti phospholipid antibodies in treating lymphomas or squamous cell carcinomas of the skin, and further use any compositions as described in WO 453 and Blackenberg to potentiate the therapeutic outcome in treating of leukemia or skin carcinomas.

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Claims 1, 3-12, 14-15, 19-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman et al (IDS, 2/14/2000) and Umeda (IDS, 9/19, 1999) in view of Haung et al Science 275: 547 - 550 1997 (IDS September 1999), and Blankenberg et al US patent 6,197,278 (IDS March 23, 2001) as directed to claims 1, 3-12, 14-15 above and further in view of Gimbrone US Patent 5,632,991 (IDS, 11/27/2000), Dovrak et al (IDS, 9/19/1999) and WO 98/29453('453) (IDS 1/24/2000) as directed to claims 19-29.

Gimbrone discloses a targeting agent conjugated to an antibody directed to ELAM-1 (E-Selectin), (col 5, lines 18-38). Gimbrone also disclose the use of his targeting agent-therapeutic agent conjugate, alone or in combination with the antibody or antibody fragment (a second anti-cancer agent), Finally, Gimbrone also disclose methods for detecting E-Selectin expression

within the body of a patient comprising steps of detecting E-Selectin by labeling the E-Selectin antibody with a radioactive isotope that can be detected under a scintillation counter, (col 18, lines 60-65). Finally, Gimbrone teach that various inflammatory cytokines such as TNF and IL-1 are able to induce the expression of ELAM-1. Gimbrone does not teach the combination therapy of the his antibody-therapeutic agent conjugate with a second anti-cancer drug.

Dovorak et al teach various strategies that would have possibly improved the delivery of monoclonal antibodies to tumor vasculature; one of which is to identify the antigen that is uniquely expressed on tumor blood vessel endothelium, (see page 82). Dovorak et al express that antibodies directed against such antigens may be linked to either metabolic poisons or to radioisotopic cytotoxic and would been expected to necrotize solid tumors by compromising their blood supply. Such teachings would have suggested to an ordinary skilled artisan how to enhance the targeting of the vascularized tumors. Dovorak has indicated that such approach offers additional advantages in that the antibodies employed need not be customized for a specific tumor (see page 83), thus providing a motivation to utilize antibodies that are directed to such antigenic sites in combination with other modalities with tumor therapy. Dovorak et al teach that the metabolic hyper permeability of tumor blood vessels in carcinomas act similar to proinflammatory mediators such as histamine in creating leaky blood vessels (page 80), and that is further analogous to the vascular hyper permeability that occurs during the wound healing process. Thus, an ordinary routiner would have concluded that the endothelial cell layer of leaky blood vessels are capable of inducing a leukocyte mediated response. Dovorak et al, however,

admit that there had been no antigens identified that would have been specific for tumor vessel endothelial surface.

Furthermore, based on the teachings of Fishmann and Umeda, one of ordinary skill in the art would have been motivated to combine the antiaminophospholipid antibodies of Blackenberger's peptide drugs directed to phosphatidylserine and a second distinct therapeutic construct such as the antibody conjugates taught by Gimbrone, because coadminsteration of a drug on the tumor cells themselves with a selective blood coagulation of tumor vasculature can improve efficacy of antivascular therapy of solid tumors as taught by Huang. Accordingly, one of ordinary skill in the art would have been motivated to coadminister the conjugates of Gimbrone with antibody's of Fishman and Umeda to target a specific tumor sites, because according to Huang, there would have been a reasonable expectation to enhance the therapeutic outcome by admistering any site specific antibodies that target tumors receptors. Respectively, preparing a therapeutic kit comprising the essential elements of such method would been obvious.

Finally, although Gimbrone et al do not fully teach the combination of his antibody-therapeutic agent conjugate with an anti-amino phospholipid antibody, one would have been motivated at the time of invention to target ELAM-1 presented on cell surface of tumor cells such as carcinomas, with a secondary antibody targeted therapeutic composition because as taught by Gimbrone the induced expression of such endothelial cell surface glycoprotein has been shown to be consistent with other inflammatory processes that are mediated by leucocytes

(such as neutrophils) and therefore, one ordinary skilled in the art would have had a reasonable expectation to succeed in improving site specific treatments of cancer cells when administering the anti-aminophospholipids of Fishmann and Umeda, with monoclonal antibody conjugates of Gimbrone et al. In fact Dvorak suggests such combination with a chemotherapeutic agent, because targeting secondary surface antigens such as ELAM-1 would have been expected to improve therapeutic outcome. Finally, preparing a therapeutic kit to conduct such method would have also been obvious for the conventional reasons of convenience & ease of use. DD 5-01

Specification

5. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Additionally, as set forth in MPEP section 608.01, an application for a patent when filed may incorporate "essential material" by reference to (1) a U.S. patent or (2) a pending U.S. application. "Essential material" is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best

mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to ...., (3) a U.S. patent or application which itself incorporates "essential material" by reference, ...See In re Fouche , 439 F.2d 1237, 169 USPQ 429 (CCPA 1971). Accordingly, the description of numerous Patented and literature publications through out the specification can not be incorporated, because they themselves contains subject matter that is incorporated by reference from another publication.

Information Disclosure Statement

6. The information disclosure statement (IDS) filed January 24, 2000, September 29, 1999, fail to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The referred IDS have been placed in the application file, but the information referred to therein has not been considered. The articles not considered are crossed out in the copy hereby submitted.

Conclusion

9. Amino phospholipid antibodies are well known in the art as has been described in the cited prior art, and one skilled in the art would expect that such antibodies as thought by Fishmann and Umeda would provide similar activity as instant antibodies disclosed in the specifications of the instant application, and accordingly, one skilled in the art would have known how to make and use the therapeutic compositions and kits thereof. However, when the intended microsphere is not as described by Fishmann and Umeda, more specifically fragments

not described in the art, the therapeutic composition would not be expected to have such properties as disclosed, and furthermore, the applicant has provided no guidance or working examples teaching one skilled in the art how to determine which type of fragments would yield the claimed invention. Therefore, based on the state of the prior art, lack of guidance and working examples, and the wide breadth of the pending claims; one skilled in the art could not use the entire scope of the claimed invention without undue experimentation.

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh, PharmD whose telephone number is (703) 306-5400. The examiner can normally be reached on Monday to Friday from 8:30 a.m. to 5:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Diana Dudash can be reached on 703-308-2328. The fax phone number for this Group is 703-308-4556. Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is 703-308-1235.

ss 5/5/2001

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